LISTING OF CLAIMS READABLE ON ELECTED SPECIES

1. (currently amended) A process for delivering a molecule to an extravascular cell in a mammalian target tissue in vivo comprising: inserting an injection solution containing the molecule into the lumen of an efferent or afferent vessel of the target tissue wherein the volume of the injection solution and the rate of injection solution insertion ~~result in~~ cause transient increased vascular permeability in the target tissue, increased ~~tissue size and~~ extravascular fluid volume within the target tissue, and extravasation of the molecule via the increased vascular permeability, [[and]] resulting in delivery of the molecule to the extravascular cell.
2. (original) The process of claim 1 wherein fluid flow out of the target tissue is occluded.
3. (original) The process of claim 1 wherein insertion of the injection solution results in increased permeability of vessels in the tissue to the molecule.
4. (original) The process of claim 1 wherein the molecule consists of a biologically active compound.
5. (original) The process of claim 1 wherein the molecule consists of a macromolecule.
6. (original) The process of claim 5 wherein the macromolecule is greater than 5 kDa.
7. (original) The process of claim 6 wherein the macromolecule is greater than 30 kDa.
8. (original) The process of claim 7 wherein the macromolecule is greater than 500 kDa.
9. (original) The process of claim 1 wherein the molecule consists of a protein.
10. (original) The process of claim 1 wherein the molecule consists of a peptide.
12. (original) The process of claim 1 wherein the molecule consists of a therapeutic molecule.
13. (original) The process of claim 1 wherein the molecule is in a complex.
14. (original) The process of claim 1 wherein the injection solution contains a compound that increase vessel permeability.
15. (original) The process of claim 14 wherein the compound consists of a vasodilator.
16. (original) The process of claim 1 wherein the cell consists of a liver cell.
17. (original) The process of claim 16 wherein the liver cell consists of a hepatocyte.
18. (original) The process of claim 1 wherein the cell consists of a skeletal muscle cell.
19. (original) The process of claim 1 wherein the cell consists of a heart muscle cell.
20. (original) The process of claim 1 wherein the cell consists of a prostate cell.

21. (original) The process of claim 1 wherein the vessel consists of a blood vessel.
22. (original) The process of claim 21 wherein the blood vessel consists of an artery.
23. (original) The process of claim 21 wherein the blood vessel consists of a vein.
24. (original) The process of claim 1 wherein the vessel consists of a bile duct.
25. (original) The process of claim 1 wherein the injection solution contains less than 20 mM salt.
26. (original) The process of claim 25 wherein the injection solution contains less than 5 mM salt.
27. (original) The process of claim 1 wherein the injection solution contains zwitterions.
29. (original) The process of claim 1 wherein the injection solution is hypertonic.
30. (currently amended) [[An]] A process for delivering a molecule to an extravascular in vivo mammalian cell in a target tissue comprising: rapidly inserting a sufficient volume of injection solution containing the molecule into the lumen of an efferent or afferent vessel of the target tissue ~~at an appropriate rate~~ and impeding fluid flow away from the tissue during the injection such that extravascular fluid volume in the tissue ~~and size of the tissue are~~ is transiently increased, resulting in swelling of the target tissue, increased vascular permeability in the target tissue, extravasation of the molecule and delivery of the molecule to the extravascular mammalian cell in the tissue.

REMARKS

Restriction:

The action states that claims 15, 20, 22, 24, and 27 by the Examiner because they are drawn to species not directed to prior art species. Applicant have received no restriction requirement with respect to these claims and have made no election with respect to these claims. Further, Applicants are unaware of any Law or Rule which permits the Examiner to withdraw any claims "as being drawn to species not directed to prior art species" and request clarification.

Minor Informalities:

The Action states that the title is objected to because it is too long as should be limited to 2-7 words. Applicants respectfully disagree. MPEP 606, "Title of Invention" states: "(a) The title of the invention may not exceed 500 characters in length and must be as short and specific as possible." Applicants' title is short (62 characters) and specific.

Rejection of the claims under 35 USC §112:

Claims 1-10, 12-14, 16-19, 21, 23, 25-26, and 29-30 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite because the phrase "…rate of injection solution insertion…" is unclear. The Action states that "a rate implies that there is a standard of time that is compared to". Applicants respectfully disagree. The volume and rate are determined by the size of the animal, size of the tissue, and size of the vessel into which the solution is injected as is described in detail on page 10 line 15 to page 11 line 21. The nature of the delivery mechanism, as described in the specification, depends on different volumes and rates being used for different animals, tissues, and vessels. Low volume or low rate do not lead to increased pressure in the vascular network that is sufficient to cause increased vascular permeability. The volume and rate is thus analogous to dosage and determining the volume and rate is thus related to determining dosage. Applicants have provided considerable guidance and examples for numerous animals, tissues and vessels: mouse liver (tail vein injection, 1.0 ml per 10 g body weight), mouse liver (bile duct injection, 1 ml), rat liver (portal vein injection, 10 ml), rat liver (bile duct injection, 5-8 ml), dog liver (bile duct injection, 200 ml), mouse hindlimb skeletal muscle (iliac injection, 2.5-3 ml), rat hindlimb skeletal muscle (iliac injection, 10-12 ml), dog limb skeletal muscle (limb

vessel injection, 50-500 ml depending on limb size), rhesus monkey limb skeletal muscle (limb vessel injection, 75-180 ml depending on limb), monkey diaphragm (inferior phrenic vein, 40 ml), mouse prostate, testis, and bladder (dorsal vein injection, 2.5 ml), pig heart (heart vessel, 20-30 ml). It is the Applicants' opinion, that from the specification and accompanying examples, it is clear that slow continuous infusion, as is used in intravenous infusion of I.V. fluids, is not within the scope of the invention. Applicants request reconsideration of this §112 rejection.

Rejection of the claims under 35 USC §102:

Claims 1-7, 9-10, 12-13, 21, 23, and 30 have been rejected under 35 U.S.C. 102(b) as being anticipated by Kim et al. (US Patent 5,346,696). '696 teaches only injection of 1 ml volume into a rat tail vein or a rabbit ear vein. For both, '696 teaches receptor mediated targeting to the liver. '696 is silent with respect to injection rate. Applicants provide, with this letter, a declaration under 37 C.F.R. 1.132 showing that injection of 1 ml volume into a rat tail vein or rabbit ear vein does not provide a sufficient volume to cause a transient increase in vascular permeability in the liver or increased extravascular fluid volume within the liver. Additionally, Applicants have amended claims 1 and 30 to more clearly distinguish the claims from the teaching of '696. Specifically, Applicants have amended the claims to recite "the volume of the injection solution and the rate of injection solution insertion cause transient increased vascular permeability in the target tissue, increased extravascular fluid volume within the target tissue, swelling of the target tissue, and extravasation of the molecule via the increased vascular permeability… ." '696 does not teach increasing vascular permeability, increasing extravascular fluid volume, swelling of the target tissue, or extravasation of the molecule via the increased vascular permeability. Support for "efferent or afferent vessel of the target tissue" can be found in the specification on page 3 lines 14-23. Support for "increased vascular permeability in the target tissue" can be found in original claim 3 and in the specification on page 8 lines 16-26 and page 11 lines 28-30. Support for "swelling of the target tissue" can be found in the specification on page 3 lines 2-12, page 49 lines 13-20, and page 64 lines 6-7. Support for "extravasation of the molecule via the increased vascular permeability" can be found in the specification on page 3 lines 2-12, and page 8 lines 32-33. Applicants request reconsideration of this §102 rejection.

Claims 1, 14, 16, 17, 25, 26, 29, and 30 have been rejected under 35 U.S.C. 102(b) as being anticipated by Veech RL (US Patent 4,663,166). '166 teaches a composition of IV fluid and is clearly directed towards IV fluid replacement. IV fluids are given to replace fluids lost by a patient when the patient is not able to properly ingest the necessary amount of fluid through normal ingestion (eating and drinking). Fluids are lost by the body normally through breathing, perspiration, urination, and stool, and abnormally through injury (blood loss) or illness (vomiting and diarrhea). It is standard practice in the art to deliver IV fluids to an individual only in an amount to replace or compensate for body fluid loss. Typical IV fluid administration has the goal of providing the patient with the "normal" amount of body fluid. Thus, for standard IV fluid replacement practice it is recommended to provide about 2000 ml over 24 hours (~0.023 ml/sec) plus additional volume for abnormal fluid loss (Parrish, Practical Gastroenterology 2007, p. 44-60, attached). The teaching of '166 is consistent with standard IV fluid replacement practice (see: column 1 lines 12-13, column 14 lines 53-55, column 18 lines 43-46, column 33 line 52 though column 34 line 6, column 35 lines 62-65). In fact, '166 teach throughout that the described composition is used to normalize body fluid (blood) composition (see: column 14 lines 53-55, column 14 lines 61-64, column 15 lines 33-39, column 15 lines 49-53, column 16 lines 62-65, and column 27 lines 55-59). There is no teaching or suggestion in '166 to provide a volume in excess of that lost by the body or to inject a solution at a rate and volume that would cause an increase in vascular permeability or extravascular fluid volume. Applicants request reconsideration of this §102 rejection.

Claims 1 and 5-8 have been rejected under 35 U.S.C. 102(b) as being anticipated by Donovan S (US Patent 6,143,306). Applicants respectfully disagree. At column 10 lines 11-13, '306 teaches "Systemic routes of administration, such as oral and *intravenous* routes of administration, are excluded from the scope of the present invention." Therefore, '306 specifically teaches away from "inserting an injection solution containing the molecule into the lumen of a efferent or afferent vessel of the target tissue". Applicants request reconsideration of this §102 rejection.

Claims 1, 18, 19, and 30 have been rejected under 35 U.S.C. 102(e) as being anticipated by Voet et al. (US Patent 6,821,520). Applicants respectfully disagree. At column 8 lines 20-21, '520

teaches "Entry of a Clostridial toxin into the circulatory system is undesirable, since botulism or tetanus can result." At column 9 lines 16-19, '520 teaches "What is needed therefore is an effective, long lasting, non-surgical resection, non-radiotherapy, *non-systemic drug administration*, therapeutic drug and method for treating Hashimoto's thyroiditis." At column 9 lines 28-32, '520 teaches "Systemic routes of administration, such as oral and intravenous routes of administration, are excluded from the scope of "local administration" of a Clostridial toxin." Therefore, '520 specifically teaches away from "inserting an injection solution containing the molecule into the lumen of a efferent or afferent vessel of the target tissue". Applicants request reconsideration of this §102 rejection.

The Examiner's rejections are now believed to be overcome by this response to the Office Action. In view of Applicants' amendment and arguments, it is submitted that claims 1-2 and 4-30 should be allowable.

Respectfully submitted,

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I hereby certify that this correspondence is being transmitted to the USPTO on this date: 11-06-2007.

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